# Structures and conformational analysis of a 3 × 3 isomer grid of nine *N*-(fluorophenyl)pyridinecarboxamides

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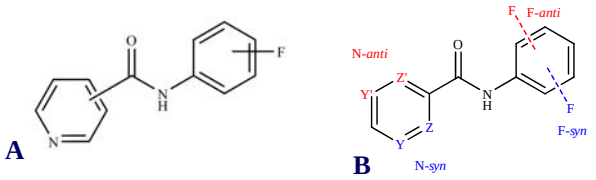
## Introduction

The synthesis and characterisation of a 3×3 isomer grid (**NxxF**) (x = *para*-/*meta*-/*ortho*-) of nine *N*-(fluorophenyl)pyridinecarboxamides (Scheme 1A, Figs. 1-3) is reported with comprehensive crystal structure (Table 1) and conformational analyses on *gas-phase* and solvated forms. The conformational features and differences between the solid-state and model conformations (*syn*/*anti*, Scheme 1B), together with structural and property trends were explored using potential energy surface (PES) diagrams (Figs. 4, 5), bridging two different areas of structural science. The influence of the aromatic group substitution patterns was also evaluated in terms of the preferred primary hydrogen bonding (N-H…N or N-H…O=C) in the solid-state, in tandem with the influence and effect of weaker interactions on molecular aggregation.[1-3]




**Scheme 1 A**. General structure diagram of **NxxF** compounds; **B**. Possible **NxxF** conformations isomers

## Experimental methods

The **NxxF** compounds were synthesised using Schotten-Baumann reaction between 4-/3-/2-pyridinoyl chlorides and 4-/3-/2-fluoroanilines. Purification was accomplished by standard organic wash up and column chromatography.

Single crystals were grown from chloroform or ethyl acetate solutions. X-ray data for all nine **NxxF** isomers were collected on an Enraf-Nonius κ-CCD diffractometer at the University of Toronto at 150(1) K (except for **NppF** at 200(1) K), θ range 2-27.5° with 100% data coverage to 25° (on θ). Data have also been collected at 294(1) K.

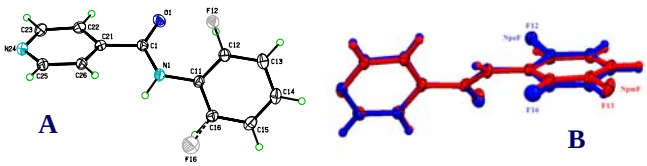



**Fig. 1 A**: The **NpoF** molecular structure with group disorder for F12 in the **F**-*anti* conformation [91.7(9)%] and F16 as **F**-*syn* [8.3(9)%]; **B**: **NpoF** and **NpmF** molecular structure overlay.

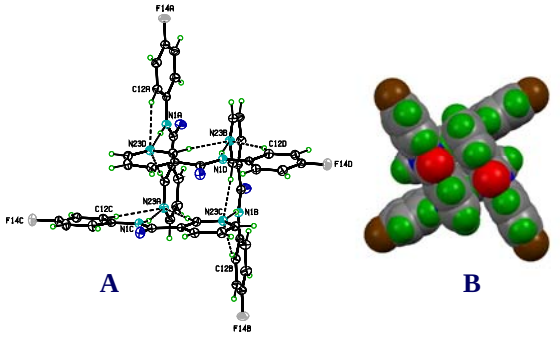



**Fig 2**. ORTEP (**A**) and CPK (**B**) diagrams of the tetrameric assembly of **NmpF** (form of "St. Brigid's Cross").

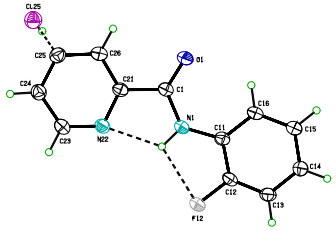


**Fig. 3** The N1-H1...N22/F12 intramolecular interactions in **NooF,** with the minor Cl site at C25.

**Table 1**. Selected crystallographic data and relevant structural features for the nine **NxxF** isomers

| NxxF | Space group | Z' | Volume (Å³) | R-factors | $C_6/C_5N$ (°) | $C_6$/amide (°) | $C_5N$/amide (°) | N…N/O (Å) | Packing |
|---|---|---|---|---|---|---|---|---|---|
| **NppF** | $P\bar{1}$ | 2 | 963.94(6) | 0.051, 0.142 | 56.74(5)<br>57.93(5) | 29.24(7)<br>33.16(6) | 27.63(7)<br>24.93(7) | 3.203(2)<br>3.216(2) | 1D chains |
| **NpmF** | *Cc* | 1 | 1032.22(10) | 0.042, 0.113 | 65.93(10) | 39.16(10) | 27.39(13) | 2.991(4) | 1D chains |
| **NpoF** | *Cc* | 1 | 1027.33(8) | 0.051, 0.135 | 76.99(12) | 51.39(12) | 27.06(15) | 2.930(4) | 1D chains |
| **NmpF** | $P\bar{1}$ | 4 | 1995.47(9) | 0.050, 0.124 | 5.42(9)<br>0.77(10)<br>5.39(9)<br>0.74(9) | 3.38(9)<br>1.99(9)<br>3.21(9)<br>1.56(9) | 2.04(9)<br>2.13(9)<br>2.18(9)<br>1.82(9) | 3.193(2)<br>3.224(2)<br>3.171(2)<br>3.254(2) | Tetrameric assembly |
| **NmmF** | $P2_1/n$ | 1 | 999.42(12) | 0.044, 0.118 | 50.16(5) | 27.47(5) | 24.00(7) | 3.1146(18) | 1D chains |
| **NmoF** | $P2_12_12_1$ | 1 | 989.44(9) | 0.049, 0.125 | 22.67(14) | 33.09(12) | 10.75(13) | 3.182(4) | 1D chains |
| **NopF** | $P2_1/c$ | 1 | 993.10(16) | 0.063, 0.166 | 30.34(10) | 27.74(11) | 4.75(15) | 2.679(3) | Intramolecular |
| **NomF** | $P2_1/n$ | 2 | 1999.17(18) | 0.074, 0.223 | 4.4(2)<br>4.6(2) | 5.5(2)<br>6.4(2) | 2.0(2)<br>4.2(2) | 2.675(4)<br>2.655(4) | Intramolecular |
| **NooF** | $P2_1/n$ | 1 | 986.32(14) | 0.057, 0.154 | 9.69(14) | 8.67(14) | 2.53(14) | 2.630(3)<br>2.654(2) | Intramolecular |

## *In silico* methods

The **NxxF** isomer optimisation and conformational analysis giving PES diagrams was performed using *ab initio* calculations (B3LYP/6-311++G, corresponding B3LYP/6-311++G** studies are in progress) on isolated (*gas-phase*) and solvated molecules (PCM-SMD solvation model with $CH_2Cl_2$ or $H_2O$ as solvents) using Gaussian03/09 together with high accuracy energy calculations (CBS-QB3) and the ΔG of solvation. Corresponding solid state structure dihedral angles were plotted in *gas phase* PES diagrams (Fig. 4) relative to optimised structures dihedral angles.

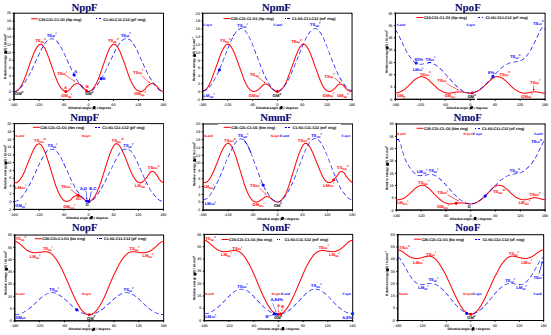



**Fig. 4** The PES conformational analysis diagrams for the **NxxF** isomers optimised in the *gas phase*: the equivalent solid state angle is depicted as a (•), with, if applicable, assigned identification letter and partial occurrence (%)

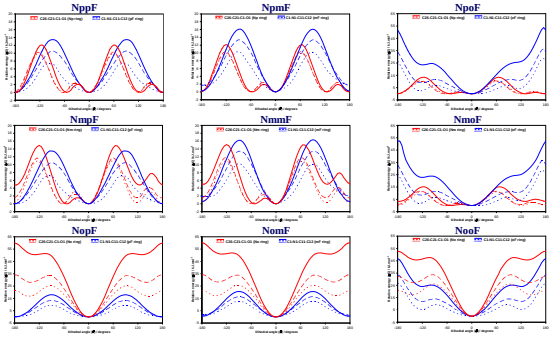



**Fig 5**. The PES conformational analysis diagrams for the nine **NxxF** isomers optimised in *gas phase* (full line), $CH_2Cl_2$ (dashed line) and in $H_2O$ (dotted line) using the PCM-SMD solvation method

## Conclusion

The molecular and crystal structures of all nine **NxxF** isomers have been determined and compared with the global minima from calculations. Eight **NxxF** structures have the $_{amide}$N-H…$N_{pyridine}$ hydrogen bond as the primary interaction with the **NppF** isomer as the only structure with aggregation *via* N-H…O=C interactions. An unusual hydrogen bonded tetramer of **NmpF** (Fig. 2) has the tetrameric assembly rationalised in terms of the directional and spatial arrangement of the N-H donor and N acceptor groups. In the last three **NoxF** molecules an intramolecular $_{amide}$N-H…$N_{pyridine}$ hydrogen bonding is observed, as well as the weaker F...H-$N_{amide}$ interaction in **NooF** (Fig. 3). Conformational analysis of optimised structures in different media allowed in-depth rationalisation and explanation of the observed disorder and energetically *meta*- or unstable conformations in solid state packing. The **NxpF** and **NxoF** modelled structures prefer the **N**-*syn*/**F**-*syn*, while **NxmF** prefers **N**-*syn*/**F**-*anti* conformation.

References:

1. D. Chopra and T. N. G. Row, *CrystEngComm*, 2008, **10**, 54-67.
2. P. Mocilac, M. Tallon, A. J. Lough and J. F. Gallagher, *CrystEngComm*, 2010, *published*.
3. P. Mocilac, A. J. Lough and J. F. Gallagher, *CrystEngComm*, 2010, *submitted*.